

claim 28 and a construct comprising an immunoglobulin protein-coding sequence which encodes a light chain or a fragment thereof, operatively linked to a promoter sequence that results in the preferential expression of the protein-coding sequence in mammary gland epithelial cells, wherein the cell expresses the light and heavy chains and secretes a heterologous, assembled immunoglobulin comprising the light and heavy chains in functional form[.] and,

wherein said promoter sequence is selected from a group consisting of: beta lactoglobulin promoter, whey acid protein promoter, and the lactalbumin promoter.

Please also see a Claims Appendix with a complete listing of the claims as amended without correction marks.

REMARKS

The Office Action of December 17, 2002 has been reviewed and its contents carefully noted. Reconsideration of this case, as amended, is respectfully requested. Applicants thank the Examiner for her thorough and detailed remarks. Claims 19, 21-23 and 25-30 are currently pending. Claims 19 and 30 are amended herein. No claims are canceled herein. No claims have been added herein.

Continued Examination under 37 CFR § 1.114

Applicants note the withdrawal of the previous Final Rejection, and the continued examination of this application pursuant to 37 CFR § 1.114. Applicants also gratefully acknowledge that the amendment of October 4, 2002 has been entered.

Claim Objection

Applicants thank the Examiner for acknowledging the effectiveness of the previous remarks regarding claims 19, 21-22, 25 and 27-30 in the last response received from the Applicant causing the withdrawal of the prior rejection under 35 U.S.C. §112, second paragraph and the Examiner's prior objection to the specification.

With specific regard to claim number 30 however, applicants believe that the objection has been rendered moot by the amendments made herein. Reconsideration is respectfully requested.

The Rejection Under 35 U.S.C. §103(a)

Meade et al., and DeBoer et al.,

Claims 19, 22-23 and 25-28 are rejected under 35 U.S.C. §103(a) as being unpatentable over the Meade et al., reference (U.S. Patent No.# 4,873,316)(hereinafter the '316 patent) and the DeBoer et al., citation (U.S. Patent No.# 5,633,076)(hereinafter the '076 patent). The rejection of the claims, as amended, is respectfully traversed.

Establishment of a *prima facie* case of obviousness is a procedural tool for allocating the burden of proof as between an Applicant and the Examiner. The initial burden is upon the Examiner to present this *prima facie* case of obviousness to negative patentability. Respectfully, in the current case the Examiner has failed to establish the needed case of obviousness, thus without more the Applicant is entitled to a grant of the patent. *In re Oetiker*, 977 F.2d 1443, 1445, 24 U.S.P.Q.2d 1443, 1444 (Fed. Cir. 1992).

A *prima facie* case of obviousness is established when the teachings from the prior art itself suggest the claimed subject matter to a person of ordinary skill in the art. *In re Bell*, 991 F.2d 781, 26 U.S.P.Q. 1529 (Fed. Cir. 1993); *In re Rijckaert*, 28 U.S.P.Q.2d 1955 (Fed. Cir. 1993).

The basic considerations which apply to obviousness rejections under MPEP § 2141 are as follows:

- (1) the claimed invention must be considered as a whole;
- (2) the references must be considered as a whole and must suggest the desirability and thus the obviousness of making the combination;

(3) the references must be viewed without the benefit of impermissible hindsight vision afforded by the claimed invention; and

(4) reasonable expectation of success is the standard by which obviousness is determined.

When the prior art itself fails to meet even one of the above criteria the cited art does not satisfy 35 U.S.C. § 103(a) and prevents the establishment of the required *prima facie* case of obviousness by the Examiner. *In re Oetiker*, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992); *In re Rijckaert*, 28 USPQ2d 1955, 1956 (Fed. Cir. 1993). In addition it must be respectfully reiterated that each of the citations indicated above fail to recognize, expressly or implicitly, any need, possibility or benefit of combining their disparate teachings in such a way that they might then read on the instant claims. Absent some teaching, suggestion, or incentive supporting this combination, a teaching that is simply not present in any of the citations provided by the Examiner, the references are objectively incapable of supporting a obviousness rejection under § 103(a). Carella v. Starlight Archery, 231 U.S.P.Q. 644 (Fed. Cir. 1986).

Moreover, obviousness is not established unless the teachings of the prior art would have suggested the claimed subject matter to a person of ordinary skill in the art with a reasonable likelihood of success of achieving the suggested invention. *In re Dow Chem.*, 5 USPQ2d 1529, 1531 (1988). Any motivation or suggestion to modify the prior art references must flow from some teaching in the art that suggests the desirability or incentive to make the modification needed to arrive at the claimed invention. *In re Napier*, 55 F.3rd 610, 613, 34 USPQ2d 1782, 1784 (Fed. Cir. 1995); *In re Gorman*, 933 F.2d 982, 986-87, 18 USPQ2d 1885, 1888 (Fed. Cir. 1991). "[I]t is not uncommon that a 'species' may be patentable, that is, satisfying sections 101-103, notwithstanding a prior art genus." *In re Ornitz & English*, 153 USPQ 458 (CCPA 1967). For example, a claim to wave guide including germanium was found to be patentable over a prior art disclosure of a wave guide including polyvalent metal dopants. Corning Glass Works v. Sumito Electric, 9 USPQ2d 1962, 1970 (Fed. Cir.1989).

As pointed out below, the prior art not only fails to provide the suggestion, or incentive to combine but also fails to provide any reasonable expectation of success for the piecemeal combination of the prior art into something resembling the instant invention. Thus, the Examiner's required *prima facie* case of obviousness respectfully cannot be established.

Meade et al.,

The Meade et al, patent provides some insight into the use of DNA constructs in transgenic animals for the production of large quantities of recombinant protein products in the milk of the altered mammals. However, the teachings of Meade et al., do not by themselves or in combination with any of the other cited art render the instant claims obvious.

Moreover, Applicants point out that claims 19, 22, 23 and 25-28 are directed to DNA constructs for providing a heterologous immunoglobulin in the milk of a non-human transgenic mammal. The constructs include a promoter sequence that results in the preferential expression of a protein-coding sequence in mammary gland epithelial cells, an immunoglobulin protein-coding sequence, a 3' non-coding sequence; and a unique restriction site between the promoter and the 3' non-coding sequence, wherein the immunoglobulin protein-coding sequence is inserted into the restriction site. Claims 29 and 30 are directed to a mammary epithelial cell which includes a DNA construct as described above encoding either an immunoglobulin light or heavy chain, and a second construct encoding the opposite immunoglobulin chain (i.e., the heavy or light chain, respectively).

Moreover, Meade et al., fails to provide or teach the following:

- a) Also as previously noted there is nothing in Meade et al. that teaches or suggests expressing the light chain and heavy chain of an immunoglobulin separately by using a mammary epithelial cell comprising at least two vectors, one encoding the heavy chain and one encoding the light chain. Meade simply fails to contemplate expressing these chains separately;
- b) Meade et al, fails to indicate that the use of two separate vectors can result in a cell capable of producing an assembled, functional immunoglobulin in milk;
- c) Meade et al., fails to disclose a unique restriction between the promoter and the 3' non-coding sequence, wherein the immunoglobulin coding sequence is inserted into the restriction site; and,
- d) Meade et al. fails to teach that the claimed construct should have a unique restriction site in between the promoter and the 3' untranslated region into

which an immunoglobulin protein-encoding sequence is inserted.

- e) The unique construction of the restriction site – such that it has a coding sequence inserted into the site- that then allows for a vector which can easily be modified, without the need for cleaving the remaining construct to insert various immunoglobulin chains is an improvement over the prior art. This allows for easier expression of a variety of different immunoglobulin coding sequences. Thus, the use a unique restriction site into which the immunoglobulin coding sequence is inserted, adapts to the unique features of expressing immunoglobulins.

This lack of guidance, that is, the lack of anything “teaching” the invention is clear. Given this, and the controlling precedent cited above, the cited are simply fails to render the instant invention obvious. Reconsideration of the rejected claims is respectfully requested.

DeBoer et al,

DeBoer et al., does not provide what Meade lacks, see “a” through “e” above. Importantly, neither Meade et al. nor DeBoer et al., teach or suggest the claimed construct having a unique restriction site in between the promoter and the 3’ untranslated region into which an immunoglobulin protein-encoding sequence is inserted. DeBoer also fails with regard to the other elements provided above.

Moreover, contrary to the Examiner’s assertions, DeBoer et al. does not make up for any of the other deficiencies of the Meade et al. reference. Specifically, the Applicants must reiterate that the Examiner asserts that Figures 5-7 of the DeBoer reference demonstrate a construct having a casein promoter and a 3’ non-coding sequence, and unique restriction sites, including XhoI, between the promoter and the 3’ coding sequence. Applicants note, however, that none of the Figures relied upon by the Examiner demonstrate a mammary gland specific promoter and a 3’ non-coding region wherein there is a unique restriction site into which the immunoglobulin-coding sequence has been inserted. As already stated DeBoer presents the state of the art as of its filing date but does not teach the invention as presented by Applicants. That is, it does not

present the elements of the current invention is clear, but it should also be noted that it simply does not teach any combination with Meade et al.

Thus, amended independent claim 19, which recites elements not rendered obvious by Meade or DeBoer alone or in combination, cannot be obvious as against either of these references. Therefore, the Examiner's rejections are traversed and reconsideration is respectfully requested. Reconsideration is respectfully requested.

Dependent claims 22, 23, and 25-28 being dependent upon and further limiting independent amended claim 19 should also be allowable for those reasons, as well as for the additional recitations they contain. Applicants respectfully request reconsideration of the rejection of claims 19, 22, 23, and 25-28 under 35 U.S.C. § 103(a) in view of the above amendments and remarks.

Vandamme et al.,

Claims 29 and 30 are rejected under 35 U.S.C. §103(a) as being unpatentable over the Meade et al., DeBoer et al., references in view of Vandamme et al. This rejection is, respectfully, improper, and should be reversed.

The limitations of the DeBoer et al., and Meade et al., citations are provided above. Moreover, with regard to claims 29 and 30 the Examiner notes that these citations "do not teach a mammary gland epithelial cell comprising two separate vectors encoding the heavy chain and light chain of the immunoglobulin" (Office Action of 12/17/02 page 5, 2nd paragraph). This while citing Vandamme et al., to make up for this deficiency. However, as pointed out below the Vandamme citation is inapposite to the instant invention, does not provide what DeBoer and Meade lack, and offer no suggestion of combination.

It is important to respectfully note that the Examiner does not provide any support to support her suggestion that the Vandamme *et al.*, an *in vitro* cell culture system could serve as an accurate approximation of the mammary gland, milk or milk protein synthesis generally, immunoglobulin assembly in a whole lactating mammary gland, or could work during established lactation in a whole animal. More important, **no one** has established an *in vitro* system where the rates of synthesis of milk components proteins, including exogenous proteins of interest, even closely approximate those found *in vivo*. More broadly no artisan has

established and maintained such an *in vitro* system. Simply put, the claims as a whole, and claims 29 and 30 specifically, recite the use of the whole animal, the Examiner attempts to apply *in vitro* cell culture data as an approximation of this whole animal system sufficient to render obvious the work of the Applicants. The two systems are simply incompatible, and not *per se* predictive of each other, in this sense they are simply non-analogous art.

Therefore, the Examiner's analysis thus inappropriately bases its rejection on the use of Vandamme et al., on the premise that one expression system and all of the interplay in the various tools used to achieve expression of a target protein or protein fragment is like another, and that therefore any cellular expression system with any given target protein is an appropriate and analogous prior art reference for the claimed invention of another such expression system. However, as the Federal Circuit has stated, "[t]wo criteria are relevant in determining whether prior art is analogous: (1) whether the art is from the same field of endeavor, regardless of the problem addressed, and (2) if the art is not within the same field of endeavor, whether it is still reasonably pertinent to a particular problem to be solved," Wang Laboratories, Inc. v. Toshiba Corp. 26 U.S.P.Q. 2d 1767, 1773 (Fed. Cir. 1993); *see also*, In re Clay, 23 U.S.P.Q. 2d 1058, 1060 (Fed. Cir. 1992); (The *Wang* court found that a prior art reference for using a nine bit controller consisting of nine memory chips encapsulated in ceramic dual in-line packages mounted on a circuit board substrate is not in the same field of endeavor as the claimed nine data memory chips for storing digital data on epoxy glass printed circuit board substrate merely because it relates to memories). Id. The Court further let stand a lower Court finding that the prior art reference was not analogous art and was not reasonably pertinent, i.e. the art would not logically have commended itself to an inventor's attention in considering his problem. Wang at 1773, and Clay at 1061. The relevance of the Wang analysis to the instant matter lies in the fact that the Vandamme reference is not only silent with regard to whole animal systems, the physiological effect of lactation hormones, and milk promoters and instead focuses and provides teaching with regard only to comparatively simple *in vitro* expression systems – essentially teaching away from the methods required to achieve success in the expression of immunoglobulins of interest in the milk of transgenic animals. Respectfully, the concerns for expression of immunoglobulin proteins and their assembly is an entirely different problem, with an entirely different set of concerns and hurdles preventing success than those inherent in the instant invention. Thus, though Vandamme might target the production of a similar protein as those provided in the instant specification, the problem addressed and the solution

provided by Vandamme et al., have little or nothing to do with the myriad of expression problems overcome by the instant claims, therefore falling outside the scope of appropriate art.

In a similar situation, the Federal Circuit concluded that as between a method and apparatus in which film is transferred to a welding station and a tape splicing machine capable of handling the same film, “[in] the light of all this evidence, one can reasonably conclude that the reference is not within the field of this inventor’s endeavor and was not directly pertinent to a particular problem with which the inventor was involved.” King Instrument Corp. v. Otari Corp., 226 U.S.P.Q. 402, 405 (Fed. Cir. 1985); *see also*, Union Carbide Corp. v. American Can Co., 220 U.S.P.Q. 584, 588 (Fed. Cir. 1984).

As in the King and Wang situations, the instant claimed invention is directed to features, methods and solutions of problems which are alien and non-analogous to the prior art cited by the Examiner. Therefore the teachings of Vandamme *et al.*, are not pertinent to the claimed invention.

Accordingly, as in *Wang* and *King*, one must conclude that Vandamme *et al.* is not within the field of this inventor’s endeavor and is not pertinent in any way to the particular problems solved by the invention as provided in claims.

More to the point, to those of ordinary skill in the art it, at the time of the present invention, it would appear that Vandamme et al., taught a difference between the *in vitro* cell culture of mammary cells, and the behavior of these same cells at the whole animal level. The consideration of Vandamme et al., cannot be done in a vacuum, the art must be considered as a whole. From this perspective the art taught away from the combination of Vandamme et al., with Meade et al., and/or DeBoer et al. These references are directly contradictory, such that one skilled in the art would not expect that Vandamme et al., would be used, compared, or would correspond to the results seen in the whole animal, or that the two studies could be combined.

Lactation is a hormonally induced condition that relies on the whole animal physiological interaction with a variety of hormones, simply to be initiated. Once milk synthesis is begun, there are considerable changes in cell morphology and metabolism not duplicated, taught, or implied by Vandamme’s *in vitro* cultures. Moreover, multiple hormonal interactions not supplied by Vandamme are needed to maintain the lactating state and produce a protein of interest. Vandamme simply is not experimenting on the same or even a similar system, and thus cannot render that system or its discoveries obvious. Whole animal experiments involve the incredibly complex web of physiologic interactions **never** approximated by cell culture research. Prolactin,

insulin and hydrocortisone are the minimal hormone mix needed to induce mammary cell differentiation and cause inactive cells to become active, but use of them in a vacuum or in an isolated culture dish does not and cannot approximate the effects on an whole animal. Thus, there is no *in vitro* system to study regulation of milk synthesis in active cells. The claims relate to established lactation in a whole animal and demonstrate elevated milk protein synthesis in the whole animal. More to the point Vandamme is simply not available for combination with any whole animal transgenic system of the type provided by Applicants.

Given the above, no obviousness rejection can be maintained based on the Vandamme *et al.*, reference. Therefore, any rejections of the claims at issue here under § 103 should be reversed, and such is respectfully requested.

Buhler et al., Bishoff et al., Gordon et al., Ebert et al., and Stinnakre et al.,

Claims 19, 21-23 and 25-28 are rejected under 35 U.S.C. §103(a) as being unpatentable over the Meade et al., DeBoer et al., references when taken in view of Buhler et al., Bishoff et al., Gordon et al., Ebert et al., and Stinnakre et al.,

As stated in a prior Response, the citations cited immediately above do not teach or suggest the claimed invention. Rather Bischoff et al., Buhler et al., Gordon et al., Ebert et al., and Stinnakre et al. are merely relied upon by the Examiner for their disclosure of specific milk protein promoters, namely whey acid promoter and lactalbumin promoter and none of these references make up for the deficiencies of Meade et al. and DeBoer et al., outlined above. Therefore, Applicants respectfully request that the Examiner withdraw this rejection.

Respectfully, the Examiner must provide more than an odd collection of references that recast pieces of known technology, and other elements that may hint at the novelty created by the Applicants in the instant invention. The Examiner must provide references that **knowingly** suggest the combination of protocols, tests, or principles, which will lead to the invention to be rendered obvious, and read upon its claims. The Examiner has not provided these references. Rather the Examiner has stated that the instant claims are obvious "to one of ordinary skill" (Office Action of December 17, 2002, page 6, last paragraph). Without more, this is a classic reproduction of the invention from improper hindsight, which cannot be used to negative

patentability or establish the required case of *prima facie* obviousness. In re Fine, 837 F.2d 1071, 1075, 5 USPQ2d 1596, 1600 (Fed. Cir. 1988).

The important point here is that with regard to the above rejections under 35 U.S.C. §103(a), it should be pointed out that to support the combination of various sources to create an obviousness rejection those sources must themselves specifically contain or objectively suggest to the skilled artisan a combination of art to achieve the invention. To allow anything less would be to render 35 U.S.C. §103(a) a subjective measure of patentability without any parameters or objective standards. This is what the Federal Circuit has squarely decided against in its statements about the improper application of hindsight to sustain an obviousness rejection. This is why the disclosures drawn upon by an Examiner must explicitly contain all the necessary techniques and suggest the combination that would lead to the invention as claimed in a factual and objective way. In re Dillon, 919 F.2d at 696, 16 USPQ2d at 1904 (Fed. Cir. 1990)(*en banc*); In re Fine, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988); In re Geiger, 815 F.2d 686, 2 USPQ2d 1276, 1278 (Fed. Cir. 1987). This the multitude of references cited by the Examiner do not do. Respectfully, the sheer number of references cobbled together do much to underscore the novelty of the instant claims.

It should be noted that in response to the Examiner's very thorough comments that existing independent claim 19 has been amended herein to address a variety of the Examiner's concerns as well as to ameliorate some structural and grammatical problems with the claims. Therefore Applicant requests reconsideration of the claims in light of these amendments and claim additions. Given the analysis above, the Examiner's remaining objections to the claims as amended are respectfully traversed. Respectfully, it is thus the objective measure of obviousness that the prior art cited of record is incapable of supporting, thus preventing the maintenance of a 35 U.S.C. §103(a) rejection. Applicants therefore respectfully request the withdrawal of the Rejection of amended claims 19, 21-23 and 25-28 under 35 U.S.C. §103(a). Reconsideration is respectfully requested.

Other than a fee for the extension of time no fee is deemed necessary in connection with the filing of this Amendment. However, the Commissioner is authorized to charge any fee which may now or hereafter be due for this application to GTC Biotherapeutics' Deposit Account No. 502092.

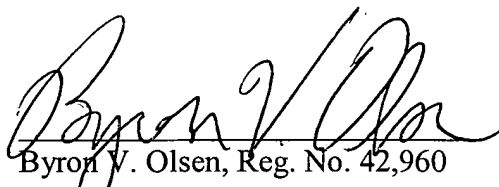
Applicants respectfully submit that the pending claims of this application are in condition for allowance, and that this case is now in condition for allowance of all claims therein. Such action is thus respectfully requested. If the Examiner disagrees, or believes for any other reason that direct contact with Applicant's attorney would advance the prosecution of the case to finality, the Examiner is invited to telephone the undersigned at the number given below.

Early and favorable action is earnestly solicited.

Respectfully Submitted,

Date: 6/17/03

By:



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Claim Appendix

19. (Twice Amended) A DNA construct for providing a heterologous immunoglobulin in the milk of a non-human transgenic mammal comprising a promoter sequence that results in the preferential expression of a protein-coding sequence in mammary gland epithelial cells, an immunoglobulin protein-coding sequence, a 3' non-coding sequence; and a unique restriction site between the promoter and the 3' non-coding sequence, wherein the immunoglobulin protein-coding sequence is inserted into the restriction site; and,
- wherein said DNA construct is integrated into the genome of said mammal in such a way that said protein-coding sequence is expressed in the mammary gland of said mammal.
21. The construct of claim 19 wherein said promoter is selected from the group consisting of the beta lactoglobulin promoter, whey acid protein promoter, and the lactalbumin promoter.
22. The construct of claim 19 wherein said immunoglobulin protein-coding sequence encodes a light chain or a fragment thereof.
23. The construct of claim 19 wherein said immunoglobulin is of human origin.
25. The construct of claim 19 wherein said promoter is the casein promoter.
26. The construct of claim 19, wherein the restriction site is an XhoI restriction site.
27. The construct of claim 19, wherein the 3' non-coding sequence is a 3' non-coding region from a mammary-specific gene.
28. The construct of claim 19, wherein the immunoglobulin protein-coding sequence

encodes a heavy chain or a fragment thereof.

29. A mammary gland epithelial cell comprising the construct of claim 22 and a construct comprising an immunoglobulin protein-coding sequence which encodes a heavy chain or a fragment thereof, operatively linked to a promoter sequence that results in the preferential expression of the protein-coding sequence in mammary gland epithelial cells, wherein the cell expresses the light and heavy chains and secretes a heterologous, assembled immunoglobulin comprising the light and heavy chains in functional form.

30. (Twice Amended) A mammary gland epithelial cell comprising the construct of claim 28 and a construct comprising an immunoglobulin protein-coding sequence which encodes a light chain or a fragment thereof, operatively linked to a promoter sequence that results in the preferential expression of the protein-coding sequence in mammary gland epithelial cells, wherein the cell expresses the light and heavy chains and secretes a heterologous, assembled immunoglobulin comprising the light and heavy chains in functional form; and,

wherein said promoter sequence is selected from a group consisting of: beta lactoglobulin promoter, whey acid protein promoter, and the lactalbumin promoter.